become available and bring us a step closer to rapid results produced by real automatic equipment with an absolute minimum of hands-on time. An increasing number of publications confirm the excellent performance of this new instrument, not only for the identification of microorganisms, but particularly for susceptibility testing. The new concept comprises the determination of a enlarged range of MICs which are then analyzed by the antimicrobial expert system which has been designed and is continuously updated by a widely accepted international panel of experts. This approach takes us a step further from simple susceptibility testing using breakpoints and closer to the oriented detection of antimicrobial resistance mechanisms, useful recommendations and closer collaboration between clinicians and microbiologists. The impact on the management of patients and on therapy has not yet been fully evaluated. In the view of worldwide cost constraints, restriction of hospital beds, shorter hospitalization time and shift to ambulatory medicine, it can be expected that more rapid and complete results will be a cornerstone of cost-efficiency. Some reorganizations of the microbiology laboratory will be necessary to optimize the possibilities offered by the VITEK 2. They adapt well to the increasing expectation of our technicians to work part-time, the extension of opening hours of laboratories and the streamlining of workflow in merging laboratories.

S81 Surveillance of antibiotic resistance: expert systems and surveillance networks

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The importance of antibiotic resistance surveillance is now recognized. It helps to control infections, to establish empirical antibiotic therapy protocols and to implement a policy of antibiotic usage. An effective surveillance system relies on the combination of an information system, automation and the ability to transfer data to other sites. A surveillance system should produce results leading to rapid and appropriate information and action. Whereas standard laboratory methods measure susceptibility or resistance to individual antimicrobials, most expert systems allow us to characterize in addition the resistance phenotypes of organisms and thus to infer resistance mechanisms. This in turn gives rise to better identification of epidemic strains or epidemic resistance mechanisms and therefore allows us to implement early infection control measures. Expert systems can also generate computer alerts, which play an important role in the early prevention of resistant organism transmission. The interest in expert systems is not limited to local surveillance and intervention but extends to national or global networks of antibiotic resistance. These networks should be supplied with homogeneous data resulting from standardized techniques. Combination of automation and expert systems tends to satisfy this requirement, since it yields reproducible and repeatable results. Finally, the use of quantitative rather than qualitative data is an additional feature of certain systems.

S82 Molecular methods for diagnostic microbiology: current and future trends

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The next generation of molecular diagnostic tests for cancer, infectious diseases and genetic predisposition will depend on multilocus genetic analysis, often involving analysis of highly complex targets or mixtures of targets. Driven in part by the expansion of the worldwide human genome projects, advances in DNA sequencing technology have resulted in systems that are easier to use and operate, at ever-decreasing cost. Genetic array technology is well suited to complex genetic analysis because of its ability to carry out multiple types of reactions, including DNA sequencing and quantitative mRNA expression analysis. This presentation will provide some examples of new molecular diagnostic paradigms that involve DNA sequencing and array-based procedures, including the identification and typing of microbes, evaluation of genetic predisposition to unusual outcomes of chronic infections, and the use of gene expression patterns to classify disease states.

S83 Influence of new diagnostic methods on clinical practice

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Currently there are major shortcomings in the laboratory definition of infection. Few community-managed infections are diagnosed with sufficient accuracy to impact on management and, in turn, to provide a more complete picture of the true epidemiology of infectious disease for the purposes of healthcare planning. Even among hospitalized patients, many infections remain undocumented or, when defined, the management of only a minority is influenced significantly. To impact on disease management more effectively, ideally new technologies should be available at the point of medical consultation, discriminate between infecting and colonizing pathogens, aid therapeutic management in a timely manner and, of course, be affordable! Rapid culture-based diagnostics will partly address these issues. However, molecular-based diagnostics have the potential for greater impact, particularly if they are specimen based and not reliant on pure culture. The clinical features of many acute infections are not sufficiently discriminating to define etiology. Thus chip technology directed at syndromes such as UTI, LRTI, URTIE, STD, SSTI, meningitis and 'jaundice' could have a major impact on disease definition and management. However, they will require new thinking with regard to the definitions of disease and endpoints of response. The future will be very interesting.

Respiratory infections: strategies for a resistance environment

S84 The resistance environment: a view from the Alexander Project

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Resistance mechanisms have emerged against all classes of antibiotics so, in the absence of novel agents, it is important that the right antibiotics are used to obtain the optimal treatment outcome, while minimizing the impact of resistance. High-quality surveillance programs, such as the Alexander Project, are necessary to monitor the prevalence of resistance and guide clinicians in their treatment choices.

Resistance in *Streptococcus pneumoniae* has become a global concern in recent years. The Alexander Project reports a high prevalence of penicillin resistance in many regions, particularly in Spain, France, Mexico, the USA and Hong Kong. The trend of resistance is upwards, even in regions where resistance has been low, such as the UK, Germany and other northern European countries. The prevalence of macrolide resistance is also increasing dramatically, and has reached significant levels (20%+) in many areas, and exceptionally high levels in South East Asia (almost 80% in Hong Kong). The prevalence of beta-lactamase-producing strains of *Haemophilus influenzae* has also increased significantly in recent years, but may be leveling off in those

countries where rates have reached 30–40%. In addition, this pathogen has low intrinsic susceptibility to macrolides. Additionally, the vast majority of *Moraxella catarrhalis* strains now produce beta-lactamase—90–100% in many regions—making many beta-lactams of limited value in empirical treatment of infections that may be caused by *H. influenzae* or *M. catarrhalis*.

These findings emphasize the need for the use of effective antibiotics to overcome the problem of resistance, the continued epidemiologic monitoring of antimicrobial resistance, both globally and locally, and the importance of reassessing current antimicrobial practice.

S85 Predicting clinical success in community respiratory tract infections

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Increasing antibiotic resistance across many parts of the world means that rational and evidence-based choices for antibiotic treatments are becoming increasingly important if the consequences of resistance are to be minimized. Prescribers may find that they need to reassess their current antibiotic choices based on criteria which can predict bacteriologic and clinical success. Animal models and clinical studies have shown that pharmacokinetic and pharmacodynamic (PD) parameters are the key to predicting optimal clinical efficacy.

For beta-lactams and some macrolides, the time for which the serum concentration exceeds the MIC is an accurate determinant of efficacy. Bacteriologic success is achieved with a time above MIC of 40% of the dosage interval for penicillins, and 50% for cephalosporins and some macrolides. For azithromycin and quinolones, AUC/MIC ratio is the key PD parameter. An AUC/MIC ratio of 25 is generally thought to predict good bacteriologic efficacy for non-serious infections in immunocompetent patients. The utility of PD parameters for predicting bacteriologic and clinical outcomes has been correlated with outcomes in otitis media and sinusitis, and confirmed in an otitis media clinical model. Using PD parameters, MIC breakpoints predictive of clinical outcome can be defined. These breakpoints, based on the serum concentration of antibiotic present for a given percentage of the dosing interval and used in conjunction with MIC data from local surveillance studies, predict the susceptibility of clinical isolates to individual antibiotics. Using these criteria, amoxycillin/clavulanate is identified as the antibiotic of choice for empirical treatment of respiratory tract infections, with the exception of infections due to atypical microorganisms.

S86 SB-265805 (SB), a potent new quinolone

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SB (LB 20304a) is a new quinolone which has an oxime-derivatized (aminomethyl) pyrrolidine substituent at C7 conferring strong Gram-positive and -negative activity plus favorable pharmacokinetics. MIC_{90} values are low against a range of respiratory pathogens when compared to other quinolones.

SB MIC_{90}s are: $<=0.06$ mg/L for group A streptococci, MSSA, *E. coli*, *Enterobacter aerogenes* and *Salmonella*; 0.12–0.25 mg/L for *Enterobacter cloacae*, *Klebsiella* spp. and *Proteus vulgaris*; $/=0.5$ mg/L for *Proteus mirabilis*, *Morganella morgani*, *Serratia*, *Citrobacter*, enterococci and MRSA. SB is bactericidal against *Streptococcus pneumoniae* (SP), *Haemophilus infuenzae* (HI), *Moraxella catarrhalis* , *Staphylococcus aureus*, *E. coli* and *Pseudomonas aeruginosa* and has a PAE of 2 h with *Staphylococcus aureus* and 19 h with *E. coli*. Compared to other new quinolones such as grepafloxacin, levofloxacin or trovafloxacin, SB is more active against quinolone-resistant HI or SP strains. A standard 20 mg/kg dose in rats resulted in a 1.5-fold greater AUC (IV dose), a 2-fold greater C_{max} and a similar $t_{1/2}$ to ciprofloxacin. SB is likely to have clinically useful activity against pathogens causing RTI, including those resistant to present quinolones.

S87 Clinical outcomes in a resistance environment

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Increasing antibiotic resistance has a negative impact on the treatment of respiratory tract infection (RTI), but the true extent of this impact has remained largely unquantified. Recent studies in acute otitis media have established the double tap methodology (tympanocentesis on day 1 and day 4-5 of treatment) as an effective clinical model, allowing investigation of the link between antibiotic resistance and antibiotic efficacy as determined by successful bacterial eradication and clinical outcome. Double tap studies show a good correlation between increasing MICs and increasing bacteriological failure rates, as well as showing correlation between bacteriological activity and clinical efficacy. Bacteriological eradication on day 4-5 gives a 97% chance of clinical success. Failure to eradicate pathogens results in clinical failure in around 40% of patients. Double tap studies also show that successful bacteriological eradication is linked to a greater improvement in clinical outcome, as shown by reduction of signs and symptoms. This clinical model confirms the need to use potent antibacterial agents that are able to eradicate the pathogen from the site of infection. Beta-lactams such as amoxycillin ±clavulanate and cefuroxime currently remain the first choice for acute otitis media based on good bacterial eradication of *Streptococcus Pneumoniae* (including intermediate penicillin-resistant strains) and *Haemophilus influenzae* (including beta-lactamase-producing strains).

Infections and cytokines

S88 IL-12 and TNF in infections

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The inflammatory cytokines IL-1 and TNF have the same spectrum of properties as bacterial products. When administered to humans, these cytokines are as toxic as bacterial products. Attention has now focused on the concept that the biological properties of IL-1 and TNF should be blocked. Blocking IL-1 or TNF has been highly successful in patients with rheumatoid arthritis, inflammatory bowel disease or graft versus host disease. However, despite a large body of animal data, anti-cytokine therapy for sepsis has been disappointing. Over 13 000 patients with septic shock have entered trials with TNF-neutralizing antibodies, soluble TNF receptors and IL-1 receptor antagonist in double-blind, placebo-controlled trials. Although there has been a highly consistent small (2–3% increase in 28-day survival with anti-cytokine therapy, the effect has not been statistically significant. Certain subgroups, such as patients with disseminated intravascular coagulation, show remarkable improvement with anti-TNF therapy. Meta-analysis of anti-cytokine therapy in sepsis concluded that the benefit was small because the sample size of each trial is small. Also, no harm appears to be associated with anti-cytokine therapy. A combination of blocking TNF and IL-1 may offer the patient with Gram-negative septic shock the greatest chance of rescue. Another approach is to treat patients with immuno-